UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/464,416	12/16/99	THANAVALA	Y RPP:156BUS

DUNN & ASSOCIATES
P O BOX 10
NEWFANE NY 14108

HM22/1023

EXAMINER	
FLOOD,M	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 10/23/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
ASSISTANT SECRETARY AND COMMISSIONER OF
PATENTS AND TRADEMARKS
Washington, D.C. 20231

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20

Application Number: 09/464,416
Filing Date: December 16, 1999
Appellant(s): Yasmin Thanavala, Charles Joel Arntzen, and Hugh S. Mason

Michael L. Dunn
For Appellant

EXAMINER'S ANSWER

This is in response to appellant's brief on appeal filed August 13, 2001.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

Claims 1, 3 and 11 have been amended subsequent to the final rejection. Claim 4 has been cancelled. Claims 1-3 and 5-12 are pending on Appeal.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that the claims do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

5,935,570	Koprowski et al.	August 10, 1999
5,914,123	Arntzen et al.	June 22, 1999

Stites et al., Basic and Clinical Immunology. 7th ed. USA: Appleton & Lange. 1991. "Chapter 58: Immunization" by Grossman et al., pages 102 and 723-741.

(10) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

Claims 1-3 and 5-12 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-3 and 5-12 stand rejected under 35 U.S.C. 112, first paragraph, because the specification while being enabling for a method of providing an immune response in a mammal to the non-enteric pathogen antigen (NEPA), hepatitis B surface antigen (HBsAg), which is induced by the oral administration of genetically altered plant material of the family *Solanaceae* expressing

the HBsAg in combination with an orally effective adjuvant, does not reasonably provide enablement for providing an immune response to a non-enteric pathogen selected from the group consisting of pathogens which cause the infectious diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever.

A method for providing immune response in a mammal that is specific to an antigen to a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in mammals free of acquired immunity to the pathogen in the absence of an oral adjuvant, said method comprising feeding the mammal with a substance comprising a physiologically acceptable material from a plant containing the NEPA, expressed by the plant in combination with an orally effective adjuvant, said combination causing an immune response to oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA alone is claimed. Dependent claims recite administering plant material that has been genetically altered to express said antigen to humans in therapeutic dose amounts over a plurality of different times, wherein said NEPA is hepatitis B surface antigen (HBsAg); wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever; and, wherein the plant material is from a plant of the family *Solanaceae,* namely a potato.

The specification broadly discloses non-enteric pathogens that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin, e.g. blood transfusions which can be used as sources of NEPA to raise a protective enteric immune response in mammals. However, the specification does not provide sufficient guidance as to how one of ordinary skill in the art would provide an immune response in a mammal and/or a human to a NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. The specification does not disclose other specific non-enteric pathogen antigens which have been subjected to the claim-designated therapeutic regimen, nor does the specification teach any methodology associated with the making of genetically altered plant materials expressing any other NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. In regard to Claim 3, the specification other than the mere suggestion on page 1, lines 13-16 does not provide guidance as to how to use the instantly claimed invention to provide an immune response to any all diseases caused by a non-enteric pathogen that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin. Thus, there is inadequate guidance as to how one of ordinary skill in the art would use the instantly claimed invention to genetically alter plant material to express any and all non-enteric pathogens other than the demonstrated HBsAg.

The art of virology, microbiology, and immunology are highly unpredictable because there are too many unknowns in the claimed process for the skilled artisan to be enabled to practice the invention at the claimed scope. Effective treatments for providing immunological responses to the instantly disclosed pathogens are relatively rare, and may be unbelievable in the absence of

supporting evidence. Claims drawn to compositions intended for the administration of compounds to humans generally require supporting evidence which clearly define the ingredients or constituents contained therein because of the unpredictability in biological responses to therapeutic treatments. In order to enable the skilled artisan to practice the invention as claimed, Appellants would have to demonstrate the functional effect and describe the effective amounts of each ingredient for the administration of the composition intended for a therapeutic treatment. Accordingly, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed plant materials expressing a non-enteric pathogen selected from those pathogens which cause the diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever, in combination with an orally effective adjuvant, which would have the claimed functional effect for providing a an immune response in a mammal, wherein the specific immune response to the NEPA was stronger than a response specific to NEPA caused by the NEPA alone.

Claims 1-3 and 5-12 stand rejected under 35 U.S.C. 103(a) as being unpatenable over Arntzen et al. (US Patent 5,914,123) in view of Koprowski et al. (US Patent 5,935,570) and Stites et al. (Stites et al., Basic and Clinical Immunology. 7th ed. USA: Appleton &

Lange. 1991. "Chapter 58: Immunization" by Grossman et al., pages 102 and 723-741). This rejection is set forth in prior Office action, Paper No. 9.

A method for providing immune response in a mammal that is specific to an antigen to a non-enteric pathogen (NEPA), the pathogen being a pathogen that invades through a breach in the skin and that does not raise a protective enteric immune response in mammals free of acquired immunity to the pathogen in the absence of an oral adjuvant, said method comprising feeding the mammal with a substance comprising a physiologically acceptable material from a plant containing the NEPA, expressed by the plant, in combination with an orally effective adjuvant, said combination causing an immune response to oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA alone is claimed. Dependent claims recite administering plant material that has been genetically altered to express said antigen to humans in therapeutic dose amounts over a plurality of different times, wherein said NEPA is hepatitis B surface antigen (HBsAg); wherein the NEPA is an antigen specific to a non-enteric pathogen selected from the group consisting of those that cause hepatitis B, hepatitis C, hepatitis delta, yellow fever, dengue hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever; and, wherein the plant material is from a plant of the family *Solanaceae,* namely a potato.

Arntzen teaches an anti-viral vaccine produced in physiologically acceptable plants, particularly the potato and the tomato, and then administered through standard vaccine procedure or by feeding the plants to a mammal or a human. Arntzen specifically teaches

methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material. Arntzen also teaches methods of making a vaccine by recovering the immunogen expressed in the plant cell for use as a vaccine. Moreover, Arntzen teaches that the physiologically acceptable plant materials expressing the HBsAg can be used both to prime the mucosal immune system and/or stimulate the humoral immune response in a dose dependent manner. See Column 3, lines 24, Columns 4-7 and Column 8, lines 1-21. In Column 11, lines 36-50, Arntzen teaches that either the parenteral or non-parenteral introduction of the taught vaccine to a mammal can elicit serum and/or secretory antibodies against the HBsAg immunogen of the vaccine with minimal induction of systemic tolerance. Arntzen further teaches a method for providing a specific immune response in a mammal to the non-enteric pathogen antigen, hepatitis B surface antigen by feeding a mammal with genetically altered physiologically acceptable plant material of a potato which is of the family *Solanaceae*. Arntzen does not teach a method for providing a specific immune response by feeding a mammal with genetically altered potato expressing a NEPA with an adjuvant, wherein the drug combination causes an immune response which is stronger than a response caused by the NEPA alone. However, it would have been obvious to one of ordinary skill in the art to combine the drug taught by Arntzen with an adjuvant because Koprowski teaches a method of making microbially transinfected plants expressing a viral antigen which can be used as an oral delivery system to elicit an immunologic response in a mammal, including a human. Koprowski further teaches that solanaceous plants can

be used as a source of physiologically acceptable material. See Column 8, lines 24-31. Koprowski also teaches that when the plant material containing the NEPA is delivered, it can be delivered with an adjuvant to facilitate or improve its immunological therapeutic activity. See Column 6, lines 22-36. One of ordinary skill in the art would have been motivated with a reasonable expectation of success that the oral delivery to a mammal, including a human, the drug taught by Arntzen with the adjuvant taught by Koprowski would induce an immune response in a mammal to the specific non-enteric pathogen, HBsAg, wherein the specific immune response was a an immune response which was stronger that a response specific to a NEPA caused by the NEPA alone due to the oral administration of genetically altered potato plant material in combination with an adjuvant because, at the time the invention was made, it was well known in the art as taught by Stites that adjuvants enhance the response of an immunogen, such as a NEPA, when the adjuvant is administered in combination with the immunogen. See page 102. Thus, the results are no more than the mere combination of known drugs administered by very old an well known methods in the art because Arntzen, as well as Stites, teach that protective immunity can be effected by the multiple administration of a vaccine over a period of time. For example, the art of immunology recognizes the routine practice of inducing immunity, acquired immunity or actively acquired immunity which is demonstrated by an antibody response that may or may not relate to specific immunity to infection or disease by vaccination or artificial immunization to provide or elicit an immune response. Thus, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success that feeding an individual

with an oral vaccine comprising genetically altered potato from the family *Solanaceae* containing HBsAg which further comprises an adjuvant would provide a stronger specific response to the NEPA than caused by the NEPA alone. Finally, one of ordinary skill in the art at the time the invention was made would have been motivated to optimize the teachings of Arntzen by providing an immune response in an individual, comprising a therapeutic regimen of ingesting the plant material in a plurality of different times and dose ranges because Arntzen teaches that a plurality of different administrations of the genetically altered plant material expressing HBsAg over separate periods of time will achieve immunization. Note that Arntzen specifically teaches that the plurality of times for the administration of the vaccines is in a range of 3 to 6, and that the time separating the vaccinations is in a range of 14 to 35 days to achieve protective levels of antibodies. See Column 15, lines 45-61. Stites also teaches that the timing of primary immunization, the interval doses, and the timing of reimmunization administrations are based on both theoretic considerations and vaccine administrations. Thus, one would have had a reasonable expectation of success to provide a therapeutic regimen such as the one in the claimed invention because the determination of an effective treatment method for providing an immune response by the oral ingestion of the claim-designated drug in combination with an orally effective adjuvant in an individual which was greater than the response elicited by the NEPA alone would have been a matter of routine optimization to one of ordinary skill in the art at the time the invention was made.

Accordingly, the claimed invention was prima facie obvious to one of ordinary skill in the art at the time the invention was made, especially in the absence of evidence to the contrary.

(11) Response to Arguments

With regard to the rejection of Claims 1-3 and 5-12 made under 35 USC 112, first paragraph, Appellants argue that there is more than sufficient teaching for making a transgenic plant required for use in accordance with the claimed invention as broadly claimed and that the present specification clearly discloses that the antigens made by such plants can function as vaccines when separated from the plant material and injected. Appellants conclude that the claimed invention is thus clearly enabled. However, Appellants' arguments are not neither persuasive nor commensurate in scope to the limitations of the claimed invention because the specification broadly discloses non-enteric pathogens that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin, e.g. blood transfusions which can be used as sources of NEPA to raise a protective enteric immune response in mammals by the oral administration of genetically altered plant material expressing a non-enteric pathogen in combination with an orally effective adjuvant rather than administration by injection, as argued by Appellant. Thus, the Office maintains that the specification does not provide sufficient guidance as to how one of ordinary skill in the art would provide an immune response in a mammal and/or a human to a NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. The specification does not disclose other specific non-enteric pathogen antigens which have been

subjected to the claim-designated therapeutic regimen, nor does the specification teach any methodology associated with the making of genetically altered plant materials expressing any other NEPA other than the non-enteric pathogen antigen, hepatitis B surface antigen. In regard to Claim 3, the specification other than the mere suggestion on page 1, lines 13-16, does not provide guidance as to how one would use the instantly claimed invention to provide an immune response to any all diseases caused by a non-enteric pathogen that invade the epidermis of mammals via punctures, abrasions, cuts or other breaches in the skin. Moreover, there is inadequate guidance as to how one of ordinary skill in the art would use the instantly claimed invention to genetically alter any and all plant material to express any and all non-enteric pathogens other than the demonstrated transgenic plant material expressing HBsAg. Given the limited showing one transgenic plant material expressing one non-enteric pathogen in combination with an orally effective adjuvant with the claimed functional effect of causing an immune response to oral administration specific to the non-enteric pathogen that is greater than a response specific to the non-enteric pathogen caused by the non-enteric pathogen alone is not sufficient to enable a claim drawn to a method for providing an immune response in a mammal that is specific to any and all non-enteric pathogens, wherein the pathogen is a pathogen that invades through a breach in the skin and does not provide in the absence of an oral adjuvant, said method comprising feeding the mammal with a substance comprising physiologically acceptable plant materials containing any and all non-enteric pathogens, as broadly claimed by Appellants.

Accordingly, it would take undue experimentation without a reasonable expectation of success to determine which amounts of the instantly claimed plant materials expressing a non-enteric pathogen selected from those pathogens which cause the diseases hepatitis C, hepatitis delta, yellow fever, dengue, hemorrhagic fever, tetanus, *Staphylococcus aureus*, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever in combination with an orally effective adjuvant, which would have the claimed functional effect for providing a an immune response in a mammal, wherein the specific immune response to the NEPA was stronger than a response specific to NEPA caused by the NEPA alone.

With regard to the rejection of Claims 1-3 and 5-12 made under 35 USC 103(a), Appellants argue that the claims are patentable over the prior art because Arntzen et al. does not teach "methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material." Instead, Appellants allege that Arntzen merely "pays lip service to raising an immune response by ingestion"; and, that ingestion of the transgenic tomato taught by Arntzen (as evidenced by the Declaration of Dr. Yasmin Thanavala made under Rule 132) does not raise any significant immune response. Thus, Appellants conclude that Arntzen fails to provide sufficient teaching, suggestion, or showing to support a rejection of the claims since Arntzen does not teach how oral immunization to HBsAg or anything else can be accomplished using a transgenic plant to raise an immune response. On page 7, lines 16-19 of the "Substitute Appeal Brief", Appellants state that

"Arntzen's suggestion of simple ingestion of plant material expressing HBsAg gives little if any immune response and certainly does not give a sufficient immune response to be considered protective. Thus, Appellants conclude that "Arntzen discloses or suggests no way in which a high immune response could be orally obtained."

With regard to Koprowski et al., Appellants argue that Koprowski neither teaches nor suggests any method for making a transgenic plant as required by the present claims. Appellants further argue that Koprowski certainly does not enable or even reasonably suggest application for orally raising an immune response (in an animal) to an antigen by oral administration of a transgenic plant, and that the suggestion of use of an adjuvant is a gratuitous statement applied across the entire non-enabled spectrum of the Koprowski' disclosure.

Finally, Appellants argue that Stites et al. adds nothing to cure the inadequate teachings of Arntzen and Koprowski because Stites does not suggest any method for orally raising a highly effective immune response in the presence of a suitable adjuvant as presently claimed.

Appellants' arguments and the declaration of Dr. Yasmin Thanavala made in Paper No. 11 filed on February 2, 2001 have been fully considered but they are not deemed persuasive because the cited references provide the suggestions and motivation to the claimed invention.

In the instant case, the primary reference of Arntzen was relied upon because Arntzen clearly teaches methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the antigen is capable of eliciting an immune response in

an animal by consumption of the physiologically acceptable plant material, particularly the potato and the tomato. In view of the showings of the Declaration made under 1.132 filed on February 1, 2001 of Paper No. 11, the Office notes the showings that the oral administration of tomatoes expressing HBsAg did not raise a discernible primary HBsAg-specific antibody response in mice. However, the patented teaching of Arntzen suggests otherwise. For example, Arntzen expressly teaches physiologically acceptable plant materials expressing HBsAg, which can be used both to prime the mucosal immune system and/or stimulate the humoral immune response in a dose dependent manner. In Column 11, lines 36-50, Arntzen teaches that either the parenteral or non-parenteral introduction of the vaccine to a mammal can elicit serum and/or secretory antibodies against the HBsAg immunogen of the vaccine with minimal induction of systemic tolerance. Moreover, Arntzen teaches that a plurality of different administrations of the genetically altered plant material expressing HBsAg over separate periods of time will provide the claimed functional effect of providing an immune response specific to the hepatitis B surface antigen to achieve immunization of a mammal. Note that Arntzen specifically teaches that the plurality of times for the administration of the vaccines is in a range of 3 to 6, and that the time separating the vaccinations is in a range of 14 to 35 days to achieve protective levels of antibodies. See Column 15, lines 45-61.

Because Arntzen does not teach a method for providing an immune response in a mammal by feeding a mammal with genetically altered potato expressing a NEPA with an orally effective adjuvant, wherein the drug combination causes an immune response which is

stronger than a response caused by the NEPA alone, the reference of Koprowski was relied upon because Koprowski does indeed teach a method of making transinfected plant material expressing a viral antigen which can be used as an oral delivery system to elicit an immunologic effect in an animal or human; and, the reference of Koprowski clearly teaches that when the vaccine is delivered for immunologic purposes, it could ve delivered with an adjuvant to facilitate or improve its immunological activity. See Column 6, lines 22-36. With regard to Appellants' argument that Koprowski does not suggest any specific adjuvant that would have the claimed functional effect, the argument is not found commensurate in scope to the limitations of the claimed invention. Finally, Stites was relied upon to demonstrate methods of providing immunological responses in individuals, as well as, the use of adjuvants to enhance the response of an immunogen, such as an NEPA, when the adjuvant is administered in combination with the immunogen.

Thus, it would have been obvious to one of ordinary skill in the art at the time the invention was made to provide a method with the claimed functional effect of raising a protective immune response in a mammal free of enteric immune response which was greater than the immune response caused by the NEPA alone, comprising the oral administration of genetically altered plant material expressing the NEPA because both Arntzen and Koprowski teach that the oral delivery of genetically and/or transinfected plant material which expresses a non-enteric pathogen antigen, such as the hepatitis B surface antigen taught by Arntzen, provide a positive humoral and/or mucosal immune response responses when delivered to a

mammal or human; and the reference of Koprowski clearly teaches that when the vaccine is delivered for immunologic purposes, it could be delivered with an adjuvant to facilitate or improve its immunological therapeutic activity. See Column 6, lines 22-36. At the time the invention was made one of ordinary skill in the art would have further motivated to add an adjuvant to the composition used in the method taught by Arntzen because Stites teaches that adjuvants enhance the response of an immunogen. Furthermore, Stites teaches that the timing of primary immunization, the interval doses, and the timing of reimmunization administrations are based on both theoretic considerations and vaccine administrations. One of ordinary skill in the art would have had a reasonable expectation of success to provide a therapeutic regimen for the oral delivery of plant material expressing a non-enteric pathogen antigen in combination with an adjuvant to provide the claimed functional effect of raising the immune response in a mammal because at the time the invention was made it was well known in the art of immunology the requisite ingredients, the requisite dose amounts of the ingredients, the requisite means for the oral administration of the ingredients, and the requisite interval times for the dose administration of the ingredients to elicit protective immunity in an individual. Thus, the results are no more than the mere combination of known drugs administered by very old and well known methods in the art of immunology because Arntzen, as well as Stites, teach that protective immunity can be effected by the multiple administration of a vaccine over a period of time; and therefore, one of ordinary skill in the art at the time the invention was made would have had a reasonable expectation of success that the instantly claimed method would provide the

claimed functional immunological effect in an animal, wherein the animal was feed the drug combination.

It should be further noted that the various proportions and amounts of the ingredients, and the plurality of times for the administration of the ingredients over periods of time used in the claimed method are result variable, and as such they would be routinely optimized by one of ordinary skill in the art practicing the inventions disclosed by each of the references. Therefore, the claim language, as broadly recited, would not preclude the skilled artisan from obtaining and/or previously providing the claimed designated therapeutic regimen beneficially taught by Arntzen and, at some later point, appropriately combining it with an orally effectively adjuvant as suggested by Koprowski and Stites.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

Michele Flood
October 18, 2001

LEON B. LANKFORD, JR.
PRIMARY EXAMINER

Michael L. Dunn
P. O. Box 10
Newfane, New York 14108

CHRISTOPHER S. F. LOW CONFEREE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Michael G. Wityshyn
Supervisory Patent Examiner
Technology Center 1600